REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-27 are pending. Non-elected claims 1-16 and 28-35 were withdrawn from consideration by the Examiner. Applicants cancel claims 28-35 without prejudice to future prosecution of that subject matter.

35 U.S.C. 102 – Novelty

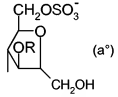
A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 17-21, 23-25 and 27 were rejected under Section 102(b) as allegedly anticipated by Oreste et al. (WO 02/50125). Applicants traverse.

WO 02/50125 discloses a process for the preparation of K5 glycosaminoglycans, comprising (i) N-deacetylation/N-sulfation of the K5 polysaccharide resulting in K5-N-sulfate, (ii) partial C5-epimerization of the carboxyl group of the glucuronic acid moiety to the corresponding iduronic acid moiety resulting in epiK5-N-sulfate, (iii) over-sulfation of epiK5-N-sulfate resulting in epiK5-amine-O-oversulfate, (iv) selective O-desulfation of epiK5-amine-O-oversulfate with a methanol/dimethyl sulfoxide mixture for a period of time from 135 to 165 minutes resulting in a partially O-desulfated epiK5-amine-O-sulfate, (v) selective 6-O-sulfation of the partially O-desulfated epiK5-amine-O-sulfate resulting in a partially O-desulfated, 6-O-sulfated epiK5-amine-O-sulfate, and (vi) N-sulfation of the partially O-desulfated, 6-O-sulfated epiK5-amine-O-sulfate resulting in the desired epiK5-N,O-sulfate. In step (iv), the selective O-desulfation initially removes sulfate groups from the 6-position of the aminosugar, then at positions 2 and 3 of the uronic acid, and finally at position 3 of the amino sugar. Products made in any of steps (ii) to (vi) may be optionally depolymerized to produce LMW products. The epiK5-N,O-sulfates have very high antithrombin activity and their glucosamine 3-O-sulfate (A-3-O-sulfate) content is from 17 to 21%.

The reactions disclosed in WO 02/50125 do not result in Applicants' claimed products, nor does WO 02/50125 provide specific reaction conditions that result in Applicants' claimed products.

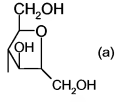
Although WO 02/50125 is silent on the chemical structure at the reducing end of the majority of the chains, one of ordinary skill in the art would have recognized that the process disclosed in WO 02/50125 (i.e., deaminative depolymerization after step (vi), followed by reduction with sodium borohydride) provides products that are characterized by the structure (a°)



(a°)

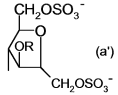
wherein R is hydrogen or SO_3^- at the reducing end of the majority of their chains as described, for example, in IT MI2002A001346 (see also PCT/IB03/02338, which was published as WO 03/106504 and is of record) which was not yet published on the effective filing date of this application, but is cited and incorporated by reference on page 7 of the present specification. In the Office Action (see especially page 6), the Examiner does not explain why the foregoing does not distinguish Applicants' claimed depolymerized-LMW-epiK5-N,O-sulfate over products in WO 02/50125.

Here, in Applicants' claimed processes, the starting epiK5-N-sulfates are characterized by the structure (a)



(a)

while all the other intermediates as well as the final products are characterized by the structure (a')



(a')

at the reducing end of the majority of their chains. The final products claimed by Applicants' have a different chemical structure and very different functional properties as compared to the corresponding LMS products described in WO 02/50125.

Finally, on the effective filing date of this application, the starting depolymerized (by nitrous depolymerization) epiK5-N-sulfates were new products because they were described for the first time in WO 03/106504, which was published on 24 December 2003 (i.e., after the effective filing date of this application). Thus, the starting products used to produce the product of claim 17 were not known in the prior art.

To summarize, Applicants' claimed products are novel over WO 02/50125. Additionally, the claimed products are nonobvious and have properties that were unexpected at the time of the effective filing date of this application. The latter is discussed below when addressing the Section 103 rejection.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by

the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 17-21, 23-25 and 27 were rejected under Section 103(a) as allegedly unpatentable over Oreste et al. (WO 02/50125). Applicants traverse. Note that "anti-IIa" and "antithrombin" are synonymous when referring to the product's activity.

As noted above, Applicants' claimed depolymerized-LMW-epiK5-N,O-sulfate is different from the products of WO 02/50125. This obviousness rejection is deficient because the *Graham* requirements were not satisfied. In particular, the Examiner failed to account for (i) the scope and content of the prior art, (ii) the level of ordinary skill in the art, and (iii) the differences between the claimed invention and the prior art. And, more importantly, no rational basis was provided in the Office Action for modifying WO 02/50125 to produce Applicants' claimed invention.

The properties of Applicants' claimed products were unexpected at the time the invention was made. They have a high content of sulfate groups in the 3-position of the glucosamine subunit, but their anti-Xa activity is much lower than that of products in WO 02/50125 because both the anti-Xa and the anti-thrombin activities of the product of Example 1 are as high as one-half those of LMW heparin (while the product of WO 02/50125 shows an anti-Xa activity more than 50% higher than that of unfractionated heparin). The whole of their properties renders Applicants' claimed products similar to LMW heparin (see paragraph [0046] of the published application). This unexpected result addresses the need for a LMW heparin-like product obtained from a non-animal source.

The advantageous and desirable properties of Applicants' claimed products as compared to the closest prior art (i.e., WO 02/50125) are clearly appreciated from the data given in the Oreste Declaration (made of record on March 21, 2008), which themselves confirm the teachings of Applicants' specification as filed. In the Oreste Declaration, the macroscopic differences in structure and properties of the product of Example 2 in WO 02/50125 and Example 1 in the present specification leap out even at a glance.

The structural differences principally reside in the unexpectedly high 3-O-sulfate content on the glucosamine subunit of products obtained through the process disclosed by Applicants in their specification and, surprisingly, in the absence of iduronic acid 3-sulfate and glucuronic acid 2-sulfate groups notwithstanding the high degree of sulfation of the claimed products as compared to the reference product (see Table 2 of Oreste Declaration).

These differences are even more evident when examining their biological activity on coagulation parameters: in particular, anti-Xa and anti-IIa activities, which are the most important parameters in the evaluation of potential antithrombotic activity, and APTT activity, which is the main parameter in evaluating anticoagulant as a whole.

Oreste's declaration explains that the product of Example 2 in WO 02/50125 is a powerful antithrombin agent while Applicants' claimed products have only weak antithrombin activity (see Table 3 of the Oreste Declaration). Moreover, the same Table 3 shows that the ratio of anti-Xa activity to anti-IIa activity of the product in WO 02/50125 is more than five times lower than that of Applicants' claimed products, which instead resembles commercially-available LMW heparin. Furthermore, Table 3 shows the anti-Xa activity/APTT activity ratio of the product in WO 02/50125 is about half that of the product from Example 1 of Applicants' specification. Thus, use of Applicants' claimed products are predicted to reduce the risk of hemorrhage in patients.

Finally, the product from Example 1 of Applicants' specification has about half of the activity of commercially-available LMW heparin for both anti-Xa and anti-IIa activities (and resulting in a similar anti-Xa activity/anti-IIa activity ratio) (see Table 2 of Oreste Declaration). Its ability to increase coagulation time is much lower than that of LMW heparin. Thus, these results confirm the teachings in the first paragraph on page 9 of

Applicants' specification (see the last sentence: "a glycosamino-glycan derived from the polysaccharide K5 that may be assimilated to the sLMWH as far as the antiXa/anti-IIa ratio is concerned and that, at equal dosages, presents a 2.5- to 4-fold lower hemorrhagic risk than sLMWH"). In summary, the Oreste Declaration confirms that the representative product of Applicants' Example 1 can be assimilated to the standard LMW heparin (sLMWH), with a lower bleeding risk. To Applicants' knowledge, their invention was the first to finally succeed in preparing a semisynthetic, LMW heparin-like product without using animal organs as the raw material.

Claims 22 and 26 were rejected under Section 103(a) as allegedly unpatentable over Oreste et al. (WO 02/50125) in view of Naggi et al. (Carbohydrate Res. 336:283-290, 2001). Applicants traverse. Oreste was discussed above. Naggi discloses an O-desulfation reaction on the generation of anti-Xa activity in heparin and LMW heparin. The cited documents do not disclose, nor do they make obvious, the O-desulfation according to Naggi study (corresponding to Step 4 of the six-step process disclosed in WO 02/50125 relating to K5 polysaccharide derivatives). It does not add anything to the disclosure of WO 02/50125.

Applicants' claim 1 comprises steps (a) to (d) which are the exact application of the above-described steps (iii)-(vi) of WO 02/50125, but applied to depolymerized LMW-epi-K5-N-sulfates (see also paragraph [0092] of the published application). It is evident that, in carrying out step (b) corresponding to step (iv), Applicants used the same procedure as described in the prior art but on a different substrate. Similarly, in paragraph [0093] of the published application, 6-O-desulfation is performed on depolymerized LMW-epiK5-amine-O-oversulfates instead of the use of polymerized substrates in WO 02/50125. The results obtained are not what would have been predicted by the skilled artisan since the product has higher A-3-O-sulfate content and much lower antithrombin activity. This appears even more surprising in view of Naggi who stated that desulfation performed at 65°C on oversulfated heparin generated sulfation patterns similar to those obtained with depolymerized, oversulfated LMW heparin (page 287, left column).

Therefore, the obviousness rejection is improper. The Oreste Declaration clearly establishes that the chemical and biological properties of Applicants' claimed products

are different from those of the products resulting from WO 02/50125 (with or without modification as proposed in the Office Action), and even opposite as far as the anti-thrombin activity in respect of LMW heparin is concerned.

Applicants contest the Examiner's allegation that the products of WO 02/51025 are structurally similar to heparin and function similarly. The target of Applicants' project begun in 1990 was to obtain a biosynthetic heparin, but the products of WO 02/51025 are not structurally similar to heparin because they have a different content in iduronic acid (i.e., about 50% against 70%), a completely different sulfation pattern (see Formula I, 17-21% 3-O-sulfated glucosamine against 0.2-1%), and a different activity profile on the coagulation parameters (i.e., much higher antithrombin activity). Applicants' claimed products, despite the fact that they are structurally very dissimilar to LMW heparin, have a biochemical profile which may be assimilated to that of the LMW heparin.

Applicants also contest the Examiner's proposal to extension the teachings of Naggi to WO 02/50125 because O-desulfation reactions when conducted on epiK5-amine-O-oversulfate or LMW fragments thereof under identical conditions unexpectedly gave a different result.

Responding to the Examiner's statement on pages 7-8 of the Office Action, the Oreste Declaration only specifically described compounds having a sulfation degree of about 2.8 because a very good LMW heparin substitute was immediately found, but they could obtain a lower sulfation degree by simply prolonging the reaction time for O-desulfation. Applicants' broader claimed range of sulfation is reasonable because:
- the obtained products are novel (both the end structure and the A-3-O-sulfate content);
- the activity is due to the high glucosamine 3-O-sulfate (A-3-O-sulfate) content;
- such high glucosamine 3-O-sulfate content is due to oversulfation, which clearly sulfates the glucosamine 3-position better than the glucosamine 3-position of the non-depolymerized epiK5-N-sulfates for these particular LMW-epiK5-N-sulfates;
- it is known that the glucosamine 3-O-sulfate group is very resistant to O-desulfation (see page 13, last paragraph, of WO 02/50125 and Table 1 of Naggi); and
- modulating the O-desulfation reaction gives products with a sulfation degree of from 2.3 to 2.7 and with a 3-O-sulfate content sufficiently high to assure the same level of

activity as that of the products with a sulfation degree of 2.7-2.9 with a reasonable expectation of success.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Double Patenting

Claims 17-27 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-3 and 35-62 of copending Application No. 09/950,003. Applicants traverse because the '003 application is abandoned according to PAIR. It appears that only Application No. 12/198,426 is still pending. Therefore, withdrawal of the double patenting rejection is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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